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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/063,978	04/21/1998	ROBERT J. OBREMSKI	45D-1750(641	5283

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/063,978	OBREMSKI ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 2, 2004 has been entered.

Amendment Entry

2. The amendment filed November 2, 2004 has been entered. Claims 1, 23, 26, 33 and 35-36 have been amended. Claims 37-42 have been newly added. Claims 1-42 are under consideration in the office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) the written description rejection of claims 1-36 under 35 U.S.C. 112, first paragraph;

b) the scope of enablement rejection of claims 1-36 under 35 U.S.C. 112, first paragraph

c) the new matter rejection of claims 1-36 under 35 U.S.C. 112, first paragraph; and

d) the rejection of claims 1-36 are rejected under 35 U.S.C. 112, second paragraph.

Response to Arguments

4. Applicant's arguments with respect to claims 1-36 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds For Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22, 26-30, 32-34, 37-38 and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The claims are drawn to a binding assay for sensing analyte mass in a liquid sample comprising a immobilization step; wherein the immobilized substrate comprises a plurality of microscopic sorbent zones wherein a zone comprises a multi-layer matrix of an analyte binding partner; a contact step; a tagging step; an illumination step; and

detection step whereby the detection of fluorescence emissions from any microscopic sorbent zone having an analyte capture complex tagged with a fluorescent label, thereby determines the analyte mass harvested from the defined volumes of sample.

The instant specification fails to provide any experiments that show the teaching of a method that determines the harvested analyte mass by simply detecting fluorescence. First, the art analyte mass detection is highly unpredictable and the instant specification fails to provide any information that the mass of any analyte could be detected in the claimed manner. Moreover, applicants' specification is a general outline of the mass assay theory drawn to a variety of assumptions and presuppositions and no actual data showing that the mass of an analyte is determined by the detection of fluorescence. Rather the specification teaches that some equations must be considered in order to determine that mass, yet the claims do not disclose the equations necessary to determine analyte mass. Moreover, the claims fail to recite steps which would enable one of skill in the art to determine analyte mass based on fluorescence detection. The claims fail to recite the necessary equilibrium conditions and ambient conditions to perform the method which determines analyte mass.

The specification teaches that the Mass Assay Theory is based on an equation, see page 8 of the instant specification. It appears that the mass assay method equation must be solved and these models and discussion are predicated on the assumption that chemical equilibrium can be reached in microscopic-scale ligand binding assays under reasonable conditions (page 8 of the instant specification) however neither the claims nor the specification recite these conditions. The mass assay theory appears to imply

that the density of the analyte, and the fluorescent signal are predicated by a quadratic solution of the mass action law assuming an affinity constant; and a mean fluorescence image intensity. See page 20 of the instant specification. However, the claims are not enabled to determine analyte mass. Moreover, it is noted that the instant specification fails to provide any examples of the detection of fluorescence emissions from any microscopic sorbent zone having an analyte capture complex tagged with a fluorescent label, which thereby determines the analyte mass harvested from the defined volumes of sample. The instant claims fail to recite any specific method steps necessary to detect and to determine the mass of an analyte based solely upon fluorescence detection.

Applicants' have failed to disclose the method steps, and the mathematical equations and manipulations necessary to determine mass. The prior art is full of teachings that teach that fluorescence detection will determine the concentration, quantity or presence of an analyte. See Ekins (J. of Clinical Immuno) which teaches fluorescently measuring the analyte concentration in the medium to which the antibody is exposed wherein the analyte binding by the antibody clearly causes analyte depletion in the surrounding medium. See also Ekins et al., (EP 304,202) who teach microscopic sorbent zones that substantially deplete analyte from the sample and concentrate the analyte onto the microsorbent zones thereby enabling fluorescently detecting the concentration of the analyte. However there is no teaching of determining analyte mass by fluorescence in the art. There is no teaching of a binding assay for sensing analyte mass in a liquid. The instant mass assay is based on an equation, which requires a

variety of assumption and presuppositions to perform a mathematical equation not disclosed by the instant claims. The specification and claims fail to enable one of skilled in the art how to distinguish between determining the presence or concentration of an analyte and determining the mass of an analyte. There are an infinite number of combinations of possible capture reagents, affinity constants, fluorescence image intensities, binding site saturation points, liquid bulk calculations, and molecules and their associated chemical equilibriums for one of skill in the art to determine as necessary to determine the mass of the analyte however, the specification fails to supply this essential information. In absence of further guidance from applicants' specification, and in view of the unpredictability and complexity in the art, it would require undue experimentation on the part of a skilled artisan to discover the key and critical characteristics of all the components which would allow one skilled in the art to determine from the plethora of procedures a binding assay for sensing analyte mass.

The claims are further drawn to conducting an assay which comprises immobilizing the substrate by non-covalent immobilization. However the instant specification at page 19 clearly states that in the mass sensing micro-assay format, the results from non-covalent immobilization have been abandoned because they were found to be susceptible to desorption and loss of capture reagent during wash steps. Moreover, covalent immobilization method found favor because signal losses in the wash steps have been found to be insignificant and the retention of bound analyte is better facilitated. Thus, it is unclear that one of skill in the art could follow these general guidelines and achieve a mass-sensing format.

There are no protocols provided which demonstrate a binding assay for sensing analyte mass in a liquid sample whereby the detection of fluorescence emissions from any microscopic sorbent zone having an analyte capture complex tagged with a fluorescent label, thereby determines the analyte mass harvested from the defined volumes of sample. Nor are their protocols detailing the determination of analyte mass harvested from the defined volumes of sample. There is merely a general outline of mass assay theory equations that do not apply directly to the instant invention. Therefore the specification fails to provide support for the claims. This demonstration is required for the skilled artisan to be able to use the claimed assay for their intended purpose of determining the analyte mass. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the analyte mass, i.e. would not be able to accurately predict analyte mass simply by detecting fluorescence emissions from any microscopic sorbent zone having an analyte capture complex tagged with a fluorescent label. Furthermore, the specification fails to adequately disclose a description of the steps for the determination of analyte mass, thus a skilled artisan would be required to de novo characterize and determine the equations necessary to determine the mass of the analyte. Accordingly, this would require undue experimentation given the fact that the specification is completely lacking in teachings as to the actual equations and procedures necessary to determine the mass of the analyte from fluorescent detection. Thus, the art indicates that it would require undue experimentation to formulate and successfully use a binding assay for sensing analyte mass.

Absent clear demonstration of the detection of fluorescence emissions from any microscopic sorbent zone having an analyte capture complex tagged with a fluorescent label, thereby determines the analyte mass harvested from the defined volumes of sample could not used in any well-established manner. Such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. The need for non-routine experimentation demonstrates the specification is not enabled for the asserted use or well-established use for determination the analyte mass. Accordingly, the specification is not enabled for using the alleged method in any manner disclosed. And, one of skill in the art would be required to perform undue experimentation to determine the analyte mass. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

6. Claims 23-25, 31, 35-36 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that there is no structural relationship between the claimed binding array and sample binding used on the array. The claims are drawn to limitations concerning the amount of analyte and the volume of the sample while failing to further limit the structural components of the binding array. Therefore the claims are rejected and clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 23-25, 35-36 and 39-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Ekins (EP 304, 202). The claims are drawn to analyte binding array comprising a plurality of microscopic sorbent zones and an analyte binding partner, wherein the zones diameter is from about 60 to 500 um and the sample contains about $10^5 - 10^{10}$ molecules of analyte per sample.

Ekins teach sample sizes at each location in an individual array may range from 10^5 to 10^{10} molecules of binding agent (page 3 lines 37-40). The support is preferably non-porous and may be made of plastic material or the support may be coated on microspheres with uniform layers of binding agents retained at specific location or in the form of a sheet or plate which is spotted with an array of dots of binding agents (page 5 lines 12-15). Thereby teaching a multi-layer matrix with the ability to vertically extend up from the surface of the substrate support. The binding agents will preferably be monoclonal antibodies which are made by well-known methods (page 5 lines 39-41). Thereby teaching that the antibodies are the analyte binding partners, just as claimed. The size of the spots is advantageously less than 10mm (page 6 line 5), thereby meeting the claimed diameter size limitation. In Example 1, the microscopic spots on

the support are approximately $1mm^2$ and a sample volume of about 400ul or 2.4×10^{10} molecules of analyte. Thus the amount of analyte binding partners are present in an amount to sufficiently deplete the analyte from the sample meeting the claimed limitations drawn to the volume of the sample from 20 to 500ul.

Therefore Ekins et al., teach an analyte binding array comprising a plurality of microscopic sorbent zones and an analyte binding partner, wherein the zones diameter is from about 60 to 500 um and the sample contains about molecules of analyte per sample.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
March 14, 2005

A. F. Smith
SUPERVISORY PATENT EXAMINER